# Addison's disease: typical and atypical presentation

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**Addison's disease (typical and atypical types)**

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Most dogs with naturally occurring hypoadrenocorticism suffer from primary hypoadrenocorticism which is also known as Addison's disease (AD). It is currently assumed that the main cause is autoimmune destruction of the adrenal cortex. At least 90% of adrenocortical tissue has to be destroyed before clinical signs become apparent. In immune mediated AD tissue loss usually takes place in a slow and progressive manner over weeks to months. Typically, the destruction involves all three zones of the adrenal cortex and results in deficiency of both cortisol and aldosterone. Cortisol is required in almost all tissues of the body and its deficiency is associated with stress intolerance, weakness, gastrointestinal signs, hypotension, absence of a stress leucogram, anemia and hypoglycemia. Aldosterone acts mainly on the renal tubule to increase the absorption of $Na^+$ and $Cl^-$ and the secretion of $K^+$ and $H^+$. Aldosterone deficiency therefore is typically characterized by variable degrees of hyperkalemia, metabolic acidosis and hyponatremia; sodium wasting in turn is associated with volume depletion. In primary hypoadrenocorticism, endogenous ACTH is highly elevated due to the negative feedback. Secondary hypoadrenocorticism is due to ACTH deficiency and has so far only rarely been described in dogs. It may result from destructive lesions in the pituitary or hypothalamus, such as neoplasia, inflammation, trauma or lymphocytic hypophysitis. Aldosterone secretion should not be impaired, as it is mainly regulated by the RAA system and the plasma potassium concentration. Differentiation between primary and secondary hypoaldosteronism is critical as the latter requires further workup (e.g. brain imaging) and prognosis may be guarded.
In primary hypoadrenocorticism (AD), the typical or classical electrolyte abnormalities are hyperkalemia and/or hyponatremia, which occur in 80 – 90% of cases. Severity of the electrolyte alterations ranges from subtle to very severe and life-threatening. It should be remembered that although hyponatremia and hyperkalemia are often seen in dogs with AD, they are not specific for the disease. They may for instance be found in dogs with primary gastrointestinal diseases (most frequently associated with diarrhoea from trichuris infection), cortisol and aldosterone concentrations are not affected in those cases.
In about 10% of dogs with AD, both sodium and potassium concentrations are within the normal range, which has been referred to as atypical AD. In those dogs, diagnosis may be delayed because the typical electrolyte changes are lacking and therefore the index of suspicion is low. When dogs with typical and atypical AD were compared, the latter were older at the time of diagnosis and had a longer duration of clinical signs which highlights the fact that the disease may go undetected for longer periods. It has been postulated that in dogs with atypical AD the destructive (e.g. immune-

mediated) process is confined to the zona fasciculata and zona reticularis, leading to an isolated glucocorticoid deficiency with intact aldosterone secretion. However, so far only very few data are available to confirm this assumption. We recently investigated cortisol and aldosterone concentrations pre and post ACTH (i.e. during an ACTH stimulation test) in 19 healthy dogs, 22 dogs with diseases mimicking AD and in 70 dogs with AD. Healthy dogs and dogs with mimicking diseases showed a significant increase in cortisol and aldosterone concentration post ACTH, whereas neither cortisol nor aldosterone increased in the dogs with AD. Interestingly, 67 of the 70 dogs with AD had low-undetectable aldosterone concentrations independent of the degree of electrolyte abnormalities, e.g. dogs with mild and dogs with severe abnormalities had similar low aldosterone concentrations. In 4 dogs with AD, the typical electrolyte abnormalities were lacking, e.g. they suffered atypical AD. The striking finding was that in all 4 dogs post-ACTH aldosterone concentrations were below the detection limit, meaning that they were able to maintain their electrolytes in the normal range without aldosterone. Our results demonstrate that normal electrolytes do not necessarily reflect a normally functioning zona glomerulosa. It is, therefore, possible that in dogs with atypical AD not only the zona fasciculata/reticularis but also the zona glomerulosa is damaged and other mechanisms (most likely intrarenal) help to maintain a normal electrolyte balance.

However, there may be exceptions as histologic evidence of partially spared zona glomerulosa has been described in a small number of dogs. Dogs with typical AD should be treated with gluco- and mineralocorticoids. In dogs with atypical AD treatment may initially be limited to the administration of glucocorticoids. However, close monitoring is of great importance as electrolyte abnormalities (and the need for additional mineralocorticoid replacement) may occur at any time during the course of disease.

With regard to work-up of cases, some important points should be considered:

1. Acute renal failure and AD may look alike as the latter often times is associated with azotemia and urine specific gravity < 1.020. Whenever azotemia is found in an acutely ill dog, the possibility of AD should be considered.
2. Most dogs with AD reveal typical electrolyte abnormalities. Hyponatremia and/or hyperkalemia should, however, not be equalized with the diagnosis of AD, as various other diseases can be associated with similar findings. Confirmation of AD requires the documentation of a low cortisol concentration after ACTH administration. A post-ACTH cortisol < 55 nmol/l is an inadequate response and consistent with AD.
3. Some dogs with AD have normal sodium and normal potassium concentrations (atypical AD). A high index of suspicion is needed as the clinical presentation is unspecific. We

routinely measure the baseline cortisol concentration in any dog with an unclear presentation. A baseline cortisol concentration > 55 nmol/l excludes the presence of AD, if cortisol is < 55 nmol/l and ACTH stimulation test is performed.

4. To differentiate between atypical AD and secondary hypoadrenocorticism, endogenous ACTH should be measured (high in case of (atypical) AD, low in case of secondary hypoadrenocorticism).
5. Diagnosis of hypoadrenocorticism is notoriously difficult in dogs which have received glucocorticoids as cortisol levels may be similarly low. Abnormal electrolytes would support the diagnosis of AD. If electrolytes abnormalities are missing, measurement of endogenous ACTH may be helpful. A very high ACTH concentration would support the diagnosis of AD, mild to moderate increases, however, may also be seen in dogs which have previously been treated with glucocorticoids.

Baumstark M, Sieber-Ruckstuhl NS, Müller C, Wenger M, Boretti FS, Reusch CE: Evaluation of aldosterone concentrations in dogs with hypoadrenocorticism. JVIM, 28, 154-159, 2014

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